

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

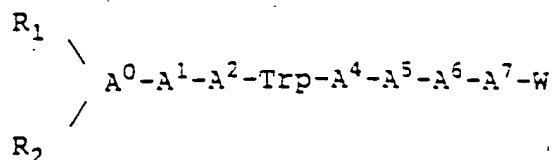
Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

1. A therapeutic peptide comprising between seven and ten amino acid residues, inclusive, said peptide being an analog of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said therapeutic peptide being of the formula:



wherein

- $A^0$  = Gly, Nle,  $\alpha$ -aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br,  $NO_2$ , OH, H or  $CH_3$ ), Trp, Cys, or  $\beta$ -Nal, or is deleted;
- $A^1$  = the D or L-isomer of any of pGlu, Nle, or  $\alpha$ -aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br,  $NO_2$ , OH, H or  $CH_3$ ),  $F_5$ -Phe, Trp, Cys, or  $\beta$ -Nal, or is deleted;
- $A^2$  = pGlu, Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br,  $NO_2$ , OH, H or  $CH_3$ ), Trp, Cys,  $\beta$ -Nal, His, 1-methyl-His, or 3-methyl-His;
- $A^4$  = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle,  $\alpha$ -aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br,  $NO_2$ , OH, H or  $CH_3$ ), Trp, Cys, or  $\beta$ -Nal;

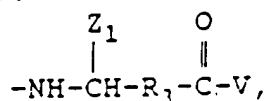
$A^5$  = Gln, Asn, Gly, Ala, Leu, Ile, Nle,  $\alpha$ -aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or  $CH_3$ ), Trp, Thr, or  $\beta$ -Nal;

$A^6$  = Sar, Gly, or the D-isomer of any of Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br,  $NO_2$ , OH, H or  $CH_3$ ), Trp, Cys, or  $\beta$ -Nal;

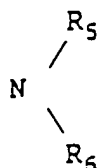
$A^7$  = 1-methyl-His, 3-methyl-His, or His;

provided that, if  $A^0$  is present,  $A^1$  cannot be pGlu; further provided that, if  $A^0$  or  $A^1$  is present,  $A^2$  cannot be pGlu; further provided that, when  $A^0$  is deleted and  $A^1$  is pGlu,  $R_1$  must be H and  $R_2$  must be the portion of Glu that forms the imine ring in pGlu; and further provided that, W can be any one of the following:

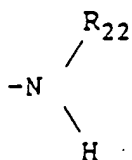
(I):



wherein  $R_3$  is  $CHR_{20}-(CH_2)_{n1}$  (where  $R_{20}$  is either of H or OH; and  $n1$  is either of 1 or 0), or is deleted, and  $Z_1$  is the identifying group of any of the amino acids Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, Gln, p-X-Phe (where X = H, F, Cl, Br,  $NO_2$ , OH, or  $CH_3$ ), F<sub>5</sub>-Phe, Trp, Cys, Met, Pro, HyPro, cyclohexyl-Ala, or  $\beta$ -nal; and V is either  $OR_4$ , or

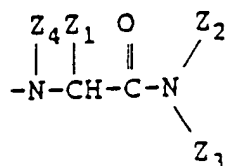


where  $R_4$  is any of  $C_{1-20}$  alkyl,  $C_{3-20}$  alkenyl,  $C_{3-20}$  alkynyl, phenyl, naphthyl, or  $C_{7-10}$  phenylalkyl, and each  $R_5$ , and  $R_6$ , independently, is any of H,  $C_{1-12}$  alkyl,  $C_{7-10}$  phenylalkyl, lower acyl, or,



where  $R_{22}$  is any of H,  $C_{1-12}$  alkyl,  $C_{7-10}$  phenylalkyl, or lower acyl; provided that, when one of  $R_5$  or  $R_6$  is  $-NHR_{22}$ , the other is H;

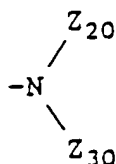
(II):



wherein  $Z_1$  is the identifying group of any one of the amino acids Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu,  $\beta$ -Nal, Gln, p-X-Phe

(where X = H, F, Cl, Br, NO<sub>2</sub>, OH or CH<sub>3</sub>), F<sub>5</sub>-Phe, Trp, Cys, Met, Pro, or HyPro; and each Z<sub>2</sub>, Z<sub>3</sub>, and Z<sub>4</sub>, independently, is H, lower alkyl, lower phenylalkyl, or lower naphthylalkyl; or

(III):



wherein each Z<sub>20</sub> and Z<sub>30</sub>, independently, is H, lower alkyl, lower phenylalkyl, lower naphthylalkyl; further provided that, when either of Z<sub>20</sub> or Z<sub>30</sub> is other than H, A<sup>7</sup> is His, A<sup>6</sup> is Gly, A<sup>5</sup> is Val, A<sup>4</sup> is Ala, A<sup>2</sup> is His, and either of R<sub>1</sub> or R<sub>2</sub> is other than H, A<sup>1</sup> must be other than deleted; further provided that, for the formulas (I) through (III), any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R<sub>1</sub> and R<sub>2</sub>, independently, is H, C<sub>1-12</sub> alkyl, C<sub>7-10</sub> phenylalkyl, COE<sub>1</sub> (where E<sub>1</sub> is C<sub>1-20</sub> alkyl, C<sub>3-20</sub> alkenyl, C<sub>3-20</sub> alkynyl, phenyl, naphthyl, or C<sub>7-10</sub> phenylalkyl), or lower acyl, and R<sub>1</sub> and R<sub>2</sub> are bonded to the N-terminal amino acid of said peptide, and further provided that when one of R<sub>1</sub> or R<sub>2</sub> is COE<sub>1</sub>, the other must be H, or a pharmaceutically acceptable salt thereof.

2. The therapeutic peptide of claim 1 wherein

$A^0$  = Gly, D-Phe, or is deleted;

$A^1$  = p-Glu, D-Phe, D-Ala, D- $\beta$ -Nal, D-Cpa, or D-Asn;

$A^2$  = Gln, His, 1-methyl-His, or 3-methyl-His;

$A^4$  = Ala;

$A^5$  = Val;

$A^6$  = Sar, Gly, D-Phe, or D-Ala;

$A^7$  = His;

and, where W is (I) and  $R_3$  is  $CH_2$  or  $CH_2-CH_2$ ,  $Z_1$  is the identifying group of Leu or Phe, where W is (I) and  $R_3$  is  $CHOH-CH_2$ ,  $Z_1$  is the identifying group of Leu, cyclohexyl-Ala, or Phe and each  $R_5$  and  $R_6$  is H; and where W is (I), V is  $NHR_6$ , and  $R_6$  is  $NH_2$ ; where W is (II),  $Z_1$  is the identifying group of any one of the amino acids Leu or p-X-Phe (where X = H, F, Cl, Br,  $NO_2$ , OH or  $CH_3$ ); and each  $Z_2$ ,  $Z_3$  and  $Z_4$ , independently, is H, lower alkyl, lower phenylalkyl, or lower naphthylalkyl; and where W is (III), each  $Z_{20}$  and  $Z_{30}$ , is H; and each  $R_1$  and  $R_2$ , independently, is H, lower alkyl, or lower acyl.

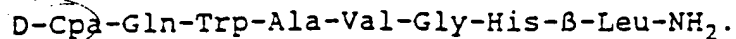
3. The therapeutic peptide of claim 2 of the formula:

D-Phe-Gln-Trp-Ala-Val-Gly-His-Leu-ethylamide.

4. The therapeutic peptide of claim 2 of the formula:

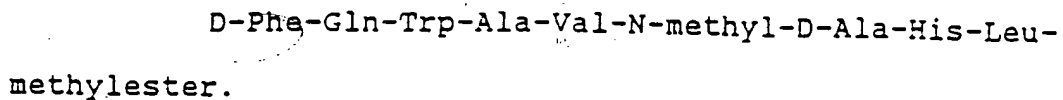
p-Glu-Gln-Trp-Ala-Val-Gly-His-statine-amide. (4)

5. The therapeutic peptide of claim 2 of the formula:



6. The peptide of claim 1 wherein W is (I), V is OR<sub>4</sub>, and R<sub>4</sub> is any of C<sub>1-20</sub> alkyl, C<sub>3-20</sub> alkenyl, C<sub>3-20</sub> alkynyl, phenyl, naphthyl, or C<sub>7-10</sub> phenylalkyl, and A<sup>6</sup> is N-methyl-D-Ala or A<sup>1</sup> is D-F<sub>5</sub>-Phe.

7. The therapeutic peptide of claim 6 of the formula:



8. The therapeutic peptide of claim 2 of the formula:

